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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,820	01/06/2006	Lars Winther	09138.0045	3909

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,820	WINTHER ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-116* is/are pending in the application.

4a) Of the above claim(s) *91,93,94 and 105-116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-90,92 and 95-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/6/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/22/06, 6/8/07, 10/28/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 88-104 in the reply filed on 10/18/2008 is acknowledged. The election of **cells** as the species of compact particle is further acknowledged. The traversal is on the ground(s) that the Office's analysis of the technical features of the invention failed to consider the inventive contribution of the support medium element (Reply, pages 2-3). In particular, Applicant argues that Dundr et al. fail to disclose a support medium (Reply, page 3). This is not found persuasive because as detailed in the previous Office action, the coverslip supporting the VLPs of Dundr et al. would be considered such a support medium (Office action mailed 7/1/2008 at page 3, first full paragraph). Therefore, it is maintained for reasons of record that unity of invention is lacking, as the technical feature linking the claimed inventions does not define a contribution over the prior art.

Applicant further argues that a search of all pending claims can be made without undue burden (Reply, pages 3-5). This is not found persuasive because Applicant is referring to the requirement to demonstrate search burden that pertains to applications filed under 35 U.S.C. 111(a) (see MPEP 801). There is no corresponding requirement to demonstrate search burden in applications filed under 35 U.S.C. 371.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 91, 93-94, and 105-116 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the

reply filed on 10/28/2008 as discussed above. Accordingly, claims 88-90, 92, and 95-104 are subject to examination below.

Priority

3. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/IB04/02682, filed 7/8/2004, which claims priority under 35 U.S.C. 119(e) from provisional application No. 60/486,381, filed 7/11/2003. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. GB 0315991.0, filed on 7/8/2003 in Great Britain.

Information Disclosure Statement

4. Applicant's Information Disclosure Statements filed 3/22/2006, 6/8/2007, and 10/28/2008 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

5. It is noted that the IDS submitted on 6/8/2007 lists four sheets (Sheet 1 of 4, Sheet 2 of 4, etc.). However, only three sheets were found in the application file. In addition, all of the Foreign Patent and Non-Patent Literature Documents submitted by Applicant on 6/8/2007 could be matched to entries listed on pages 1-3 of the IDS. The Examiner therefore presumes that only three IDS sheets were in fact submitted, and that the reference to sheet 4 was a typographical error.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 88-90, 92, and 95-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 88 recites "a compact particle comprising a quantity of detectable entity attached to the compact particle **and supported by the medium**" (emphasis added). It is unclear due to the grammatical structure of the claim whether "supported by the medium" is intended to modify "compact particle" or "detectable entity". As such, it is unclear whether Applicant intends that the compact particle, or only the detectable entity is supported by the medium

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 88-90, 92, 95-96, and 98-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Battifora et al. (U.S. 5,610,022).

Battifora et al. teach an internal control or standard for quantitative assay by immunohistochemistry of target molecules (i.e., reference standard for a detectable entity), comprising cells (i.e., compact particles) that express a known amount of a target molecule such

as estrogen or progesterone receptor (i.e., detectable entities). The instant specification defines the term "attached" so as to encompass any association between the detectable entity and the compact particle, e.g. intracellular detectable entities (see page 64, lines 1-14 and page 52), such that the target molecules expressed by cells as in Battifora et al. would be considered to be "attached" to the cells. The cells are embedded in a gel (i.e., support medium). See in particular the abstract; column 1, lines 51-56; column 2, lines 10-24; column 3, line 12 to column 4, line 15; and Examples I-II.

With respect to claim 92, Battifora et al. teach that the target molecules may be indicative of an abnormal condition (column 1, lines 23-27).

With respect to claims 95-96, Battifora et al. teach that the target molecules were detected in slices or cross-sections (i.e., defined regions). See Example 1.

With respect to claim 100, the presence of the target molecules may be revealed by binding to specific antibodies (see, e.g., column 14, lines 31-32 and 52-53).

With respect to claim 101, the embedding medium has a box shape as the mold containing the gel is rectangular (Figures 1-2 and column 2, lines 10-24).

With respect to claims 102-103, the reference standard may comprise a plurality of layers each comprising different known amounts of the antigen (column 2, lines 14-24). Since the same cells and the same antigens are involved, but that the amount of antigen is varied among layers, this would mean that the density of the antigen is different in different layers.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 97 is rejected under 35 U.S.C. 103(a) as being unpatentable over Battifora et al. in view of Lodish et al. (Molecular Cell Biology, Fourth Edition (2000), W.H. Freeman, New York, NY, sections 17.5, 23.4, and 23.7; and Figures 17-25 and 23-25; retrieved from http://www.ncbi.nlm.nih.gov/books on 1/27/2008).

Battifora et al. is as discussed in detail above. The reference teaches a reference standard substantially as claimed, but fails to specifically teach that the detectable entities (target molecules/ antigens) include those that are covalently attached to the compact particle (cell).

Nonetheless, Battifora et al. make explicit that their method is not limited to the receptors exemplified, teach that internal controls can be applied for "any desired molecules" to

be quantified in a specimen, including proteins expressed by oncogenes, cell growth factors, receptor molecules, etc. (see column 3, lines 29-44 and column 5, lines 56-60).

Lodish et al. teach that there are a vast array of integral membrane proteins, and that some of these proteins are covalently attached to the membrane via a GPI anchor (see in particular section 17.5, the first two paragraphs and the section "After Insertion in the ER Membrane, Some Proteins Are Transferred to a GPI Anchor"; and Figure 17.25.

Lodish et al. further teach known GPI-anchored proteins of interest, including GDNFR-α, a protein involved in growth and branching of the uteric bud (see section 23.4, in particular the section entitled "Activation of the Ret Receptor Promotes Growth and Branching of the Uteric Bud"). In addition, Ephrin A ligands are also attached covalently to the cell membrane via a GPI Anchor (see especially section 23.4, "Cell-Surface Ephrin Ligands and Receptors Mediate Reciprocal Induction during Angiogenesis"; Figure 23-25; and section 23.7, "Ephrin A Ligands Are Expressed as a Gradient along the Anteroposterior Tectal Axis"). These ligands play a crucial role in forming connections between neurons in the developing nervous system (section 23.4).

The teachings of Lodish et al. indicate that proteins covalently attached to cells were known in the art, and that such proteins were of recognized importance in cell growth and development.

Therefore, it would have been obvious to one of ordinary skill in the art to modify the internal control of Battifora et al., which is designed for the purpose of direct quantitative assay by immunohistochemistry of target antigens, for quantitative assay of GPI-anchored proteins (which are covalently attached to cells) as the type of detectable entity/ target molecule. In

particular, it would have been obvious to prepare an internal control having embedded cells expressing a known amount of a GPI-anchored protein of interest. One would have been motivated to do this in order to prepare a reference standard for detection of a GPI-anchored protein of interest in a quantitative manner. More generally, one would be motivated to develop reference standards for assay of GPI-anchored proteins because of their recognized role in cell growth and development.

Motivation to combine the reference teachings in this manner is also found in Battifora et al., which directs the skilled artisan to quantify target molecules or antigens that are cell growth factors or molecules that control cell proliferation. One would have had a reasonable expectation of success because Battifora et al. teach that their invention can be applied to any desired molecules simply by selection of appropriate cell lines.

14. Claim 104 is rejected under 35 U.S.C. 103(a) as being unpatentable over Battifora et al. in view of O'Leary et al. ("Standardization in immunohistochemistry", Appl Immunohistochem Mol Morphol. 2001 Mar;9(1):3-8).

Battifora et al. is as discussed in detail above, which teaches a reference standard substantially as claimed, but which fails to specifically teach the inclusion of a positive control that comprises a compact particle with substantially no detectable entity.

O'Leary et al. relates to standardization of immunohistochemical analysis, and teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible (page 5, last paragraph).

Negative controls comprise tissues or cells that do not contain the antigen to be detected (Table 5).

Therefore, it would have been further obvious to include cells that do not contain the target molecule/ antigen to be detected (i.e., detectable entity) as negative controls as taught by O'Leary et al. in the reference standard of Battifora et al. One would be motivated to do this in order to allow for standardization of immunohistochemical analyses in which the reference standard is used, based on the explicit teachings by O'Leary et al. that such negative controls should be included whenever possible in immunohistochemistry (which is the analysis method for which the reference standard of Battifora et al. is designed).

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 88-90, 92, 95-96, and 98-103 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-32 and 35-41 of copending Application No. 10/547,033 in view of Battifora et al.

The claims of Application No. 10/547,033 recite a reference standard comprising (i) a support medium; and (ii) a quantity of at least one detectable entity supported by the support medium (see, e.g., claims 1, 36, and 40).

The claims of Application No. 10/547,033 differ from instant claim 1 in that the copending application does not recite that the detectable entity is attached to a compact particle such as a cell.

Battifora et al. (discussed above) teaches reference standards that include detectable entity provided in the context of cells (i.e., compact particles) that express a known amount of the detectable entity (target molecule). The cells are embedded in a gel (i.e., support medium). See in particular the abstract; column 1, lines 51-56; column 2, lines 10-24; column 3, line 12 to column 4, line 15; and Examples I-II.

Therefore, it would have been obvious to one of ordinary skill in the art to provide the detectable entities in the reference standard of Application No. 10/547,033 in the context of cells expressing the detectable entities, and to embed such cells in the support medium. Combination of the prior art elements in this manner according to known methods (as taught by Battifora et al.) would have performed the same function, namely as a reference standard.

This is a provisional obviousness-type double patenting rejection.

17. Claim 97 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-32 and 35-41 of copending Application No. 10/547,033 in view of Battifora et al. as applied to claim 88 above, and further in view of Lodish et al.

Copending Application No. 10/547,033 and Battifora et al. are as discussed above, which fail to specifically teach that the detectable entities (target molecules/ antigens) include those that are covalently attached to the compact particle (cell).

However, in light of the teachings of Lodish et al. discussed in detail above, it would have been obvious to one of ordinary skill in the art to modify the internal control of Application No. 10/547,033 and Battifora et al. for quantitative assay of GPI-anchored proteins (which are covalently attached to cells) as the type of detectable entity. In particular, it would have been obvious to prepare an internal control having embedded cells expressing a known amount of a GPI-anchored protein of interest. One would have been motivated to do this in order to prepare a reference standard for detection of a GPI-anchored protein of interest in a quantitative manner.

This is a provisional obviousness-type double patenting rejection.

18. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-32 and 35-41 of copending Application No. 10/547,033 in view of Battifora et al. as applied to claim 88 above, and further in view of O'Leary et al.

Copending Application No. 10/547,033 and Battifora et al. are as discussed above, which fail to specifically teach the inclusion of a positive control that comprises a compact particle with substantially no detectable entity.

O'Leary et al. relates to standardization of immunohistochemical analyses, and teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible (page 5, last paragraph). Negative controls comprise tissues or cells that do not contain the antigen to be detected (Table 5).

Therefore, it would have been further obvious to include cells that do not contain the target molecule/ antigen to be detected (i.e., detectable entity) as negative controls as taught by O'Leary et al. in the reference standard of Copending Application No. 10/547,033 and Battifora et al. One would be motivated to do this in order to allow for standardization of immunohistochemical analyses in which the reference standard is used, based on the explicit teachings by O'Leary et al. that such negative controls should be included whenever possible in immunohistochemistry (which is the analysis method for which the reference standard of Battifora et al. is designed).

This is a provisional obviousness-type double patenting rejection.

19. Claims 88-90, 92, 95-96, and 98-103 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26, 31, 33-40, 44-45, and 48-52 of copending Application No. 11/884,247. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No.

11/884,247 also claims a matrix (i.e., support medium) in which microparticles or cells may be embedded (see, e.g., claims 1 and 34-36. The microparticles or cells are associated with (i.e., attached to) detectable entities ("antigens") such as CD3 or CD4 (see claims 15 and 34-36).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-32 and 35-41 of copending Application No. 11/884,247 in view of O'Leary et al.

Copending Application No. 11/884,247 is as discussed above. The claims of the copending application recite a reference standard (matrix with embedded cells or microparticles) substantially as claimed but do not recite a positive control that comprises a compact particle with substantially no detectable entity.

O'Leary et al. relates to standardization of immunohistochemical analyses, and teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible (page 5, last paragraph). Negative controls comprise tissues or cells that do not contain the antigen to be detected (Table 5).

Therefore, it would have been further obvious to include cells that do not contain the target molecule/ antigen to be detected (i.e., detectable entity) as negative controls as taught by O'Leary et al. in the reference standard of Copending Application No. 11/884,247. One would be

motivated to do this in order to allow for standardization of immunohistochemical analyses, which is the analysis method invoked by the claims of the copending application.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641